Perspectives in Diabetes

Omega-3 Fatty Acids in Diabetes Mellitus

Gift from the Sea?

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The potential role of omega-3 fatty acids in the prevention of atherosclerotic disease in the nondiabetic population currently engenders interest, enthusiasm, and controversy. Some apparently beneficial effects of omega-3 fatty acids on platelet function, eicosanoid formation, plasma triglyceride levels, and blood pressure have been described in patients with diabetes mellitus. However, enthusiasm for the use of omega-3 fatty acids in diabetes has been dampened by reports of potentially deleterious effects of these agents, including increased plasma glucose, glycosylated hemoglobin, plasma total cholesterol and LDL cholesterol, and serum apolipoprotein B levels. These adverse effects have been achieved with large, perhaps excessive, doses of omega-3 fatty acids, in the range of 4–10 g/day. The magnitude of these adverse effects has been small (typically 10–36%). It cannot be assumed that the effects of omega-3 fatty acids are the same in patients with diabetes mellitus as in nondiabetic subjects or patients with primary hyperlipidemia. First, the biosynthesis and composition of fatty acids is abnormal in diabetic animals and possibly in diabetic patients. Second, many potential mechanisms implicated in the pathogenesis of atherosclerosis are present in diabetic but not necessarily in nondiabetic subjects. Third, the mechanisms of many of the risk factors in diabetic patients differ from the mechanisms of these abnormalities in nondiabetic subjects, reflecting the effects of insulin deficiency, hyperglycemia, and their sequelae. Finally, because diabetes is a heterogeneous group of diseases, the effects of omega-3 fatty acids must be addressed separately for patients with insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, and possibly other forms of diabetes. Thus, it is not possible to assess the potential risks and benefits of dietary fish and fish oils in diabetic patients. Studies are needed to determine the regulation of fatty acid synthesis and the fatty acid composition of phospholipids in diabetic patients under defined conditions of metabolic control and diet and to determine the effects of dietary fish and fish oils in appropriate quantities on the fatty acid composition of phospholipids, the mechanisms involved in the pathogenesis of vascular disease in diabetes, and the incidence of microvascular and atherosclerotic complications. *Diabetes* 38:539–43, 1989

The potential role of omega-3 fatty acids in the prevention of atherosclerotic disease in the nondiabetic population elicits great interest and enthusiasm among the scientific community and the public at large and considerable controversy with regard to dietary and pharmacological recommendations. The initial enthusiasm for this gift from the sea was soon followed by warnings about potentially deleterious effects unique to diabetic patients, e.g., worsening of hyperglycemia. What is the potential role of these marine lipids in the prevention of atherosclerotic disease and microvascular disease in patients with diabetes mellitus? The purpose of this article is to specify the kinds of information needed to answer this question and to assess the information available about the risks and benefits of omega-3 fatty acids in diabetes mellitus.

DIETARY POLYUNSATURATED FATTY ACIDS AND VASCULAR DISEASE

The idea that the consumption of dietary fish or fish oils rich in omega-3 fatty acids may exert a beneficial effect on human health first attracted widespread attention because of studies of the dietary composition of the Greenland Eskimos, a population with a low prevalence of atherosclerosis and an age-adjusted mortality rate from acute myocardial infarction that is ~10% that of the inhabitants of Denmark or North America, despite the fact that Greenland Eskimos consume

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as much fat and cholesterol as the Danes and the North Americans (1–4). The major difference was in the composition rather than the quantity of the dietary fats (2,3). The Danes consumed more than twice as much saturated fat and more omega-6 fatty acids than the Eskimos. The Eskimos consumed ~14 g/day of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived predominantly from the seals and whales that are major components of the Eskimo diet. These provocative observations were made while the involvement of platelets and eicosanoids in the pathogenesis of atherosclerosis was being recognized.

It was quickly appreciated that dietary omega-3 fatty acids might alter eicosanoid synthesis and decrease platelet function and thereby decrease the risk of atherosclerosis. The appeal of the hypothesis grew with the recognition that omega-3 fatty acids not only modify platelet function and eicosanoid synthesis but also affect many other mechanisms involved in the pathogenesis of atherosclerosis (4,5). In other words, the prophylactic value of omega-3 fatty acids is potentially high because they act at multiple steps implicated in the pathogenesis of atherosclerosis (4,5). Omega-3 fatty acids inhibit arachidonic acid synthesis and incorporation into phospholipids, decrease platelet production of thromboxane A_2 (TXA_2), a potent vasoconstrictor and inducer of platelet aggregation, and increase production by platelets of TXA_3, which lacks biological activity. EPA is used for synthesis of prostaglandin I_3 (PGI_3), the activity of which is added to that of PGI_2, a potent vasodilator and inhibitor of platelet aggregation. Other proposed effects of omega-3 fatty acids include decreased platelet aggregation (and possibly other platelet functions), decreased plasma lipoprotein levels, increased deformability of the erythrocyte, decreased blood viscosity, decreased blood pressure, decreased blood pressure response to vasopressors, increased thrombolytic activity, alterations in leukotriene production, and decreased inflammatory cell activity. The effects of omega-3 fatty acids in the nondiabetic population have recently been reviewed (4–6).

Thus, a single dietary manipulation may modify multiple mechanisms involved in the pathogenesis of atherosclerotic disease. Because some of these mechanisms contribute to the development of diabetic microvascular disease, it is a reasonable corollary that omega-3 fatty acids may also delay or prevent the development of diabetic microvascular disease.

HAZARDS OF EXTRAPOLATION FROM NONDIABETIC TO DIABETIC PATIENTS

It cannot be assumed that the effects of omega-3 fatty acids are the same in patients with diabetes mellitus as in nondiabetic subjects or patients with a primary hyperlipidemia. First, the biosynthesis and composition of fatty acids is abnormal in diabetic animals and possibly in diabetic patients. Second, many potential mechanisms of atherosclerosis, e.g., hyperglycemia, increased platelet aggregation and platelet TXA_2 synthesis, and decreased erythrocyte deformability (with a consequent increase in blood viscosity), are present in diabetic but not necessarily nondiabetic subjects. Third, the mechanisms of many of the risk factors in diabetic patients, e.g., hyperlipidemia, increased platelet aggregation, and decreased erythrocyte deformability, differ from the mechanisms of these abnormalities in nondiabetic subjects, reflecting the effects of insulin deficiency, hyperglycemia, and their sequelae. Finally, because diabetes mellitus is a heterogeneous group of diseases, the effects of omega-3 fatty acids must be addressed separately for patients with insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), and perhaps other forms of diabetes.

ABNORMAL FATTY ACID COMPOSITION OF PLASMA AND TISSUE LIPIDS IN DIABETES

The biosynthesis and composition of fatty acids in phospholipids is abnormal in diabetes (Fig. 1). Fatty acid composition is altered in the phospholipids of various tissues in experimental animals with diabetes mellitus, including plasma, liver, heart, kidneys, and erythrocytes (7–12). These changes probably reflect decreased activities of the microsomal Δ^9-desaturase, Δ^6-desaturase (7,8,12), and Δ^5-desaturase (10,12) enzymes. The Δ^9-desaturase enzyme converts saturated fatty acids into monounsaturated fatty acids. The Δ^6-desaturase converts linoleic acid to γ-linolenic acid; this is the rate-limiting step in the conversion of linoleic acid to arachidonic acid. The Δ^5-desaturase converts dihomo-γ-linolenic acid to arachidonic acid and eicosatetraenoic acid to EPA, which can be converted to DHA. Thus, these enzymes are necessary for the biosynthesis of arachidonic acid, EPA, DHA, and other unsaturated fatty acids.

In relative terms, the arachidonic acid content is often decreased and the omega-3 fatty acid content (including EPA and DHA) is often increased in the tissue phospholipids of diabetic rats (10). In absolute terms (based on measurements of the fatty acids of the total lipids in the carcass of the whole animal), all polyunsaturated fatty acids (omega-6 and omega-3) are decreased in diabetes (10).

Insulin therapy reverses and overcorrects the diminished Δ^9- and Δ^6-desaturase activities and restores the fatty acid composition to normal, except for the decrease in arachidonic acid (8,12). Furthermore, the changes in fatty acid composition in diabetes are influenced by diet, because restriction of food intake decreases the magnitude of these changes (8,10). Thus, the alterations in fatty acid composition in tissues from diabetic animals reflect the consequences of insulin deficiency and diet. The arachidonic acid deficiency in some tissues, e.g., platelets, could also reflect enhanced phospholipase activity and enhanced release and utilization of arachidonate.

These observations have been made in the rat. Studies on the fatty acid composition of platelets derived from diabetic patients have produced seemingly inconsistent findings. For example, arachidonic acid levels have been either decreased (13), increased (14–16), or unchanged (17–19). The extant studies have not been controlled for the degree of insulin deficiency or for the composition of the diet.

These findings have several implications. First, because fatty acid synthesis and composition are altered in diabetes, the effects of dietary modifications may be different in diabetic than in nondiabetic individuals. For example, if in relative terms arachidonic acid content is decreased and omega-3 fatty acid content is increased in diabetic patients (as is the case in animals), then additional supplementation

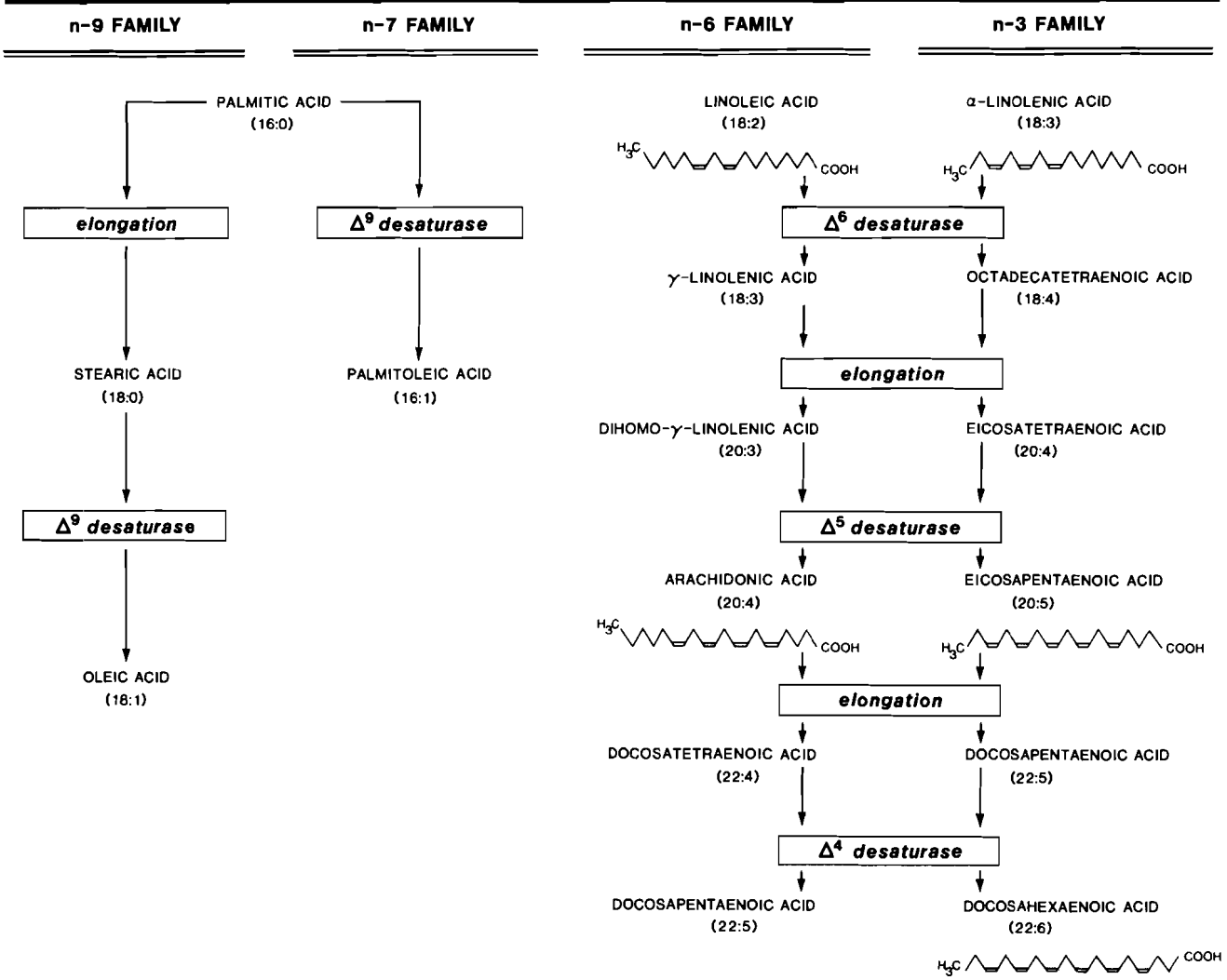

FIG. 1. Pathways of metabolism of fatty acids by chain elongation and desaturation. Fatty acids are divided into 4 families: n-9, n-7, n-6, and n-3 (or ω-9, ω-7, ω-6, and ω-3). Number in each family name indicates position of 1st double bond, counting from methyl end of molecule. Chemical formula indicates number of carbon atoms and then number of double bonds. For example, arachidonic acid contains 20 carbon atoms and 4 double bonds: 1st is located after C-6, counting from methyl end. Chemical formula may also include location of 1st double bond counting from methyl end. Thus, arachidonic acid is also rendered frequently as 20:4 n-6, where number after n indicates position of 1st double bond, counting from methyl end. Spatial configurations of selected fatty acids are also depicted. Fatty acids are converted from one to another by sequence of elongation and desaturation steps. Desaturase enzymes are named by position at which double bond is introduced, counting from carboxyl end of molecule. Abnormalities in these pathways in diabetic animals are reported to occur at Δ^9-desaturase, Δ^6-desaturase, and Δ^5-desaturase steps (see text).

with omega-3 fatty acids may be of little benefit. Alternatively, if in absolute terms all polyunsaturated fatty acids (omega-6 and omega-3) are decreased in diabetic patients (as is the case with animals), then the net balance of omega-6 and omega-3 fatty acids and their biologically active products may be unusually susceptible to dietary manipulation in diabetic patients. Second, studies are needed in patients with diabetes to determine *1*) the fatty acid composition of phospholipids under defined conditions of metabolic control and diet and *2*) the effects of fish and fish oils on phospholipid fatty acid composition under these conditions.

EFFECTS OF OMEGA-3 FATTY ACIDS IN DIABETES MELLITUS RELATIVE TO DOSE

Several studies of the effects of omega-3 fatty acids in diabetes mellitus have already been performed. Some apparently beneficial effects of omega-3 fatty acids on platelet function, eicosanoid formation, plasma triglycerides, and blood pressure have been described (20–23). For example, 4.6 g/day of omega-3 fatty acids produced a significant reduction in platelet TXB_2 production in vitro and in the lag phase of platelet aggregation but not in the extent of aggregation in patients with IDDM (20). Approximately 1.6 g/day of omega-3 fatty acids administered in the form of cod liver oil decreased TXB_2 generation by clotting blood in patients with IDDM but not in normal subjects (21). A dose of 9 g/day of omega-3 fatty acids decreased platelet aggregation and circulating triglyceride levels in patients with NIDDM (22). A dose of 2.7 g of omega-3 fatty acids appeared to decrease both the systolic and diastolic blood pressure in patients with NIDDM (23).

The enthusiasm displayed initially among investigators and in the news media for omega-3 fatty acids in diabetes was rapidly superseded by warnings about the potentially

deleterious effects of these agents, including increases in plasma glucose (24–28), glycosylated hemoglobin (25,26), plasma total cholesterol and low-density lipoprotein cholesterol (LDL-chol) (20,27), and serum apolipoprotein B (apoB) (23,26) levels. In general, the magnitude of these changes has been small (typically 10–36%). The changes in glucose metabolism are associated with increased hepatic glucose output, impaired insulin secretion, and unchanged glucose disposal rates (25). The total cholesterol and LDL-chol levels did not change in some studies (23–26). The increases in apoB levels are not specific for diabetic patients, because they also occur in nondiabetic subjects (29). The modest increases in plasma glucose and glycosylated hemoglobin levels probably could be prevented by conventional treatment for diabetes, i.e., other modalities of diet, oral hypoglycemic agents, or insulin. Thus, it may be possible to obtain the beneficial effects of omega-3 fatty acids without a deterioration of metabolic control. This possibility has not been investigated.

The putative adverse effects of omega-3 fatty acids have almost invariably been achieved with large doses (4–10 g/day). (An exception to this statement is a study that employed 2.7 g/day of omega-3 fatty acids per day but lacked a control group or a washout period [23].) These doses correspond to 0.33–0.83 kg (0.73–1.83 lb)/day of fish that is rich in omega-3 fatty acids, assuming a content of 1.2 g omega-3 fatty acids/100 g of fish (4,30). These doses are large in terms of the amount of fish that a person can reasonably be expected to eat and in terms of the benefits that have been ascribed to fish consumption vis-à-vis death from coronary heart disease. Thus, a recent study of a group of Dutch men described an inverse relationship between fish consumption and death from coronary heart disease during a 20-yr follow-up period (31). Mortality from coronary heart disease was >50% lower among those who consumed fish than among those who did not. The benefits of fish consumption were detected among subjects who consumed ≥30 g of fish per day, estimated to contain 0.2 g of EPA. Interpretation of this study depends on a dietary history obtained at the start of the 20-yr follow-up period and on the assumption that fish consumption remained relatively constant during this interval. Many of the effects of omega-3 fatty acids, such as their effects on plasma triglycerides and glucose metabolism, are related to dose in diabetic patients (26). An intake of 4 g/day in patients with NIDDM appears to have no effect on fasting plasma glucose and glycosylated hemoglobin levels (20,26).

These considerations suggest that the doses of omega-3 fatty acids used in patients with diabetes mellitus have been excessive and that beneficial effects may be achieved and potentially harmful effects may be averted at lower doses. Alternatively, the beneficial effects of dietary fish may not be due entirely to the presence of omega-3 fatty acids. This possibility seems unlikely, because virtually all of the known effects of fish on risk factors for vascular disease are reproduced by omega-3 fatty acids, but it has not been excluded (4). Excessive doses of omega-3 fatty acids are no more rational than excessive doses of aspirin in efforts to prevent vascular disease. The dose of omega-3 fatty acids that will give the optimal ratio of beneficial effects to harmful ones is unknown. Whether small quantities taken over a prolonged period will produce the same effects as large quantities consumed over a brief period is also unknown. The relationship between dose and effect, a matter of fundamental importance in nutrition and pharmacology, must be defined for dietary fish and fish oils in patients with diabetes mellitus. The few studies of the effects of omega-3 fatty acids that have been performed in patients with diabetes mellitus do not define the role of these lipids in this disorder. Rather, they help to define the direction of future studies.

Studies are urgently needed to assess the effects of lower and more realistic doses of omega-3 fatty acids (provided as dietary fish or fish oils) on risk factors for vascular disease in diabetes to determine whether such doses will favorably alter some risk factors, e.g., platelet function and eicosanoid production, without having a deleterious effect on other risk factors, e.g., plasma glucose levels and lipoprotein metabolism. These investigations should also be controlled for the fat and calorie content of the fish or fish oils under study. The quantity of fish or fish oils administered should be related to the patient's size (e.g., body mass index), and studies should be performed for prolonged periods (months or years) to determine whether any observed effects are transient or long lasting.

From this discussion, it appears that it will be difficult to predict the effect of omega-3 fatty acids on the incidence of macrovascular and microvascular complications in diabetes, because the pathogenesis of these complications involves multiple variables, some that may change in an apparently favorable direction and others in an apparently deleterious way in response to these marine lipids. Whereas studies of the effects of omega-3 fatty acids on the mechanisms implicated in the pathogenesis of diabetic vascular complications are essential to an understanding of the biological effects of these substances, such studies probably will not reveal the net effect of omega-3 fatty acids on the incidence of vascular complications. There is no substitute for direct ascertainment of the effects of omega-3 fatty acids on the incidence, prevalence, and severity of vascular disease in patients with diabetes mellitus.

TABLE 1
Areas for future study of omega-3 fatty acids in diabetes mellitus

- The regulation of fatty acid synthesis and the fatty acid composition of phospholipids in plasma, platelets, and other tissues under defined conditions of metabolic control and diet
- The effects of dietary fish and fish oils in appropriate quantities on:
  1. phospholipid fatty acid composition of plasma, platelets, and other tissues
  2. potential pathogenetic mechanisms
     —platelet function
     —eicosanoid (prostaglandin, thromboxane, and leukotriene) production
     —lipoprotein and apolipoprotein levels
     —erythrocyte deformability
     —blood viscosity
     —blood pressure
     —thrombolytic activity
     —inflammatory cell activity
  3. incidence of vascular complications
     —microvascular: retinopathy, nephropathy, and certain neuropathic complications
     —atherosclerotic

CONCLUSIONS

It is not yet possible to assess the potential risks and benefits of dietary fish and fish oils in patients with diabetes mellitus. Studies are needed to determine the regulation of fatty acid synthesis and the fatty acid composition of phospholipids in diabetic patients under defined conditions of metabolic control and diet. Studies are also needed to determine the effects of dietary fish and fish oils in appropriate quantities on the fatty acid composition of phospholipids, the mechanisms involved in the pathogenesis of vascular disease, and the incidence of microvascular and atherosclerotic complications in patients with diabetes mellitus (Table 1).

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